REMARKS

Claims 1-3, 5-32, 37, 38 and 118-120 were pending. Claims 22, 31 and 32 have been cancelled. New claims 121-124 have been added. Accordingly, Claims 1-3, 5-21, 23-30, 37, 38 and 118-124 will be pending upon entry of the present amendment.

Claims 1, 5, 30 and 37 have been amended to specify that the recited oligopeptide is linked at its amino terminus to a negatively charged or neutral stabilizing group which reduces the toxicity of the claimed compound or conjugate. Support for this amendment can be found, for example, in the specification as originally filed at least at page 16, lines 1-18. New dependent claims 121-124 have been added and recite language previously in pending independent claims 1, 5 and 37. Accordingly, no new matter has been added.

Claim 13 has been amended to delete amino acid sequences subject to a restricton requirement. All of the amino acid sequences in pending claim 13 contain the core sequence βAla-Leu-Ala-Leu. Cancellation of the other amino acids sequences is made without prejudice to further prosecution in one or more divisional applications.

The foregoing cancellation of and amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections, and have been made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application.

Objection to the Specification

The Examiner has objected to the specification for failing to comply with 35 U.S.C. §§ 119(e) and 120. Accordingly, the specification has been amended to specific reference to the priority applications. An amended application data sheet is also being submitted concurrently herewith.

Rejection of Claims 30 and 32 under 35 U.S.C. § 102(b)

Claims 30 and 32 have been rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,962,216 ("'216"). According to the Examiner, '216 describes a tetrapeptide linked to doxorubicin.

Applicants respectfully traverse this rejection. As amended, claim 30 and its dependent claims are directed to conjugates comprising an oligopeptide of the formula $(AA)_n$-AA^4-AA^3-AA^2-AA^1, wherein: each AA independently represents an amino acid, n is an integer from 0 to 16, AA^4 represents a non-genetically-encoded amino acid, AA^3 represents any amino acid, AA^2 represents any amino acid, and AA^1 represents any

amino acid, wherein the oligopeptide is cleavable by TOP, the oligopeptide is linked to a therapeutic agent and the oligopeptide is linked to a negatively charged or neutral stabilizing group at the amino terminus of the oligopeptide.

'216 does not teach or suggest conjugates which have negatively charged or neutral stabilizing groups at the amino terminus of the oligopeptide, as presently claimed. Therefore, Applicants respectfully request withdrawal of the rejection of claims 30 and 32 under 35 U.S.C. § 102(b).

Rejection of Claims 30-32 under 35 U.S.C. § 103(a)

Claims 30-32 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over '216, in view of Li *et al.* (*J. Biol. Chem.* (1990) 235, 2638-2641) and DeJongh *et al.* (*Biomed. Mass Spec.* (1976) 3, 191-195). Claim 30 and its dependent claims have been described above. Claims 31 and 32 have been cancelled, thus rendering their rejection moot.

According to the Examiner, while '216 describes a tetrapeptide linked to doxorubicin, Li *et al.* and DeJongh *et al.* each teach N-succinyl peptide derivatives. The Examiner further asserts that "DeJongh *et al.* describes that the terminal amino group may be blocked by a reaction with succinic anhydride, and that this product may further be derivatized for mass spectroscopy analysis. Li *et al.* describes that succinylation of peptide hormones led to a decrease in hormone activities."

Applicants respectfully traverse this rejection. Presently pending claims 30-32 encompass conjugates with a neutral or negatively charged stabilizing group which were not only not taught or suggested by the prior art at the time of the invention, but also were non-obvious over the prior art for at least the reasons described below.

The claimed conjugates have different and unexpected properties compared to conjugates without neutral or negatively charged stabilizing groups. Specifically, as shown in Applicants' specification, the presently claimed conjugates possess unexpected functional properties compared to conjugates without a neutral or negative stabilizing group. This is evidenced for example, by the sharp reduction of acute toxicity of N-succinylated βAla-Leu-Ala-Leu-Dox, as compared to the non-succinylated βAla-Leu-Ala-Leu-Dox. Such reduced toxicity could not have been predicted over the teachings of the prior art nor did the prior art provide any reasonable expectation of success in achieving a conjugate having such reduced toxicity.

Indeed, Applicants note that the conjugates described in '216 were found to be acutely toxic. For example, when non-succinylated βAla-Leu-Ala-Leu-Dox was administered to five mice at a dose of 174 μMol/ml, all five mice died as described in

Example 23 on pages 64-65 of the specification. In contrast, Applicants made the surprising discovery that by attaching a neutral or negatively charged stabilizing group to the conjugate, the acute toxicity of the conjugates were reduced. Specifically, in Example 23 on page 65 of the present specification, Applicants show that capping the terminal amino group of βAla-Leu-Ala-Leu-Dox with a negatively charged moiety resulted in the complete disappearance of the acute toxicity at dose levels as high as 250 mg Dox-HCl, eq./kg.

The reduction of acute toxicity of the conjugates of the invention could not have been predicted in view of the teachings of the prior art. The primary reference, '216, does not even recognize the acute toxicity of non-succinylated conjugates, let alone suggest a solution to this problem, as discovered by Applicants. Accordingly, '216 fails to provide sufficient motivation or reasonable expectation of success in making the presently claimed invention. The secondary references of DeJongh *et al.* and Li *et al.* fail to make up for the deficiencies of the '216 patent. Indeed, DeJongh *et al.* merely teaches that succinylating peptides may be useful for analytical purposes, but neither teaches nor suggests that succinylation at the N-terminal would be useful in a non-analytical setting for reducing toxicity. Moreover, there was no motivation to combine the teachings of DeJongh et al. with those of the '216 patent, since there is no suggestion in the '216 patent or elsewhere to conduct mass spectroscopy analysis on the peptide compounds described therein, which is the only purpose for which DeJongh *et al.* teach succinylation of peptides. Furthermore, Li *et al.* merely teaches that N-succinylation reduces the rate of hydrolysis of peptide hormones, whereas the '216 patent does not teach that the peptide compounds described therein are hormones and thus, again, there would be no motivation to combine the teachings of Li *et al.* with those of the '216 patent. Significantly, neither DeJongh *et al.* nor Li *et al.* teach or suggest reducing acute toxicity by adding a negatively charged or neutral stabilizing group to the conjugate of the invention, as claimed by Applicants. Therefore, a skilled artisan would not have been able to arrive at the claimed invention using the teachings of '216 in combination with DeJongh *et al.* and Li *et al.*, nor would have been motivated to have tried.

For at least the foregoing reasons, Applicants respectfully request that this rejection of claims 30 and 32 under 35 U.S.C. § 103 (a) be reconsidered and withdrawn.

Rejection of Claims 1-3, 5-9, 12-19, 22, 23, 25, 26, 28, 30-32, 37, 38 and 118-120 under 35 U.S.C. § 103(a)

Claims 1-3, 5-9, 12-19, 22, 23, 25, 26, 28, 30-32, 37, 38 and 118-120 are rejected under 35 U.S.C. § 103(a) as being unpatentable over '216, as applied above, in

combination with Li *et al.* and DeJongh *et al.*, each as applied above, and in further view of U.S. Patent No. 4,376,765 ("'765"), U.S. 2003/0119021 ("Koster"), and WO 91/11457 ("Buckley *et al.*"). Claims 22, 31 and 32 have been cancelled, thus rendering their rejection moot.

Claims 1, 5, 30 and 37 and their dependent claims are directed to compounds, conjugates and pharmaceutical compositions comprising an oligopeptide which is linked at its amino terminus to a negatively charged or neutral stabilizing group which reduces the toxicity of the claimed compound.

Applicants respectfully traverse this rejection. As described above, the presently claimed compounds have unexpected reduced toxicity *in vivo* compared to compounds without neutral or negatively charged stabilizing groups, and thus are unobvious and patentable over the teachings of '216 in combination with Li *et al.* and DeJongh *et al.*. The additional teachings of '765, Koster, and Buckley *et al.* fail to make up for the deficiencies.

As described above, '216 describes tetrapeptides linked to doxorubicin, but fails to provide any motivation to succinylate such tetrapeptides. Furthermore, DeJongh *et al.* merely suggests that succinylating peptides may be useful for analytical purposes. DeJongh *et al.* neither teaches nor suggests that succinylation at the N-terminal would be useful in a non-analytical setting or provides any motivation to combine its teachings with those of the '216 patent. Li *et al.* merely suggests that N-succinylation reduces the rate of hydrolysis of peptide hormones and, again, provides no motivation to combine its teachings with those of the '216 patent. Significantly, neither DeJongh *et al.* nor Li *et al.* teach or suggest that the acute toxicity of oligopeptide compounds linked to therapeutic agents can be reduced by adding a negatively charged or neutral stabilizing group to the amino terminus, as claimed by Applicants. Furthermore, neither DeJongh *et al.* nor Li *et al.* provide any teachings which would have allowed an ordinarily skilled artisan to predict the that the use of a negatively charged or neutral stabilizing group would result in greatly reduced acute toxicity of the compounds of the invention.

The '765 reference also fails to provide any motivation or reasonable expectation of success in achieving the presently claimed invention. This reference describes various succinylated peptides of the formula X-Leu-Drug and stipulates that X is 1-3 amino acids, and that the resulting conjugates are stable to blood circulation, and disassociate or cleave in target cells. While one example of a succinylated peptide described by the '765 patent is BSA-suc-Ala-Leu-Ala-Leu-doxorubicin, the use of succinyl in this peptide is limited to use as part of the spacer between the carrier hormone and the spacer arm, not as a negatively charged or neutral stabilizing group at the amino terminus of the peptide,

which unexpectedly reduces toxicity *in vivo*, as presently claimed. Nor does '765 provide any motivation to have used succinyl or another neutral or negatively charged stabilizing group as presently claimed. In contrast, '765 teaches attaching positively charged BSA to the succinyl group.

Koster and Buckley also fail to make up for the deficiencies in the primary reference. The Examiner relies on Koster to show that "those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (Koster, page 8, column 2)." The Examiner relies on Buckley *et al.*, to show that βAla and Ala are "both neutral, small, non-polar amino acids and are deemed to be conservative substitutions based on size, charge and polarity." However, these references, alone or in combination, also fail to teach or suggest the claimed compounds or the unexpected functional properties of the claimed compounds. Indeed these references are silent with respect to using a negatively charged or neutral stabilizing group to reduce acute toxicity.

For at least the foregoing reasons, Applicants respectfully request that the rejection of claims 1-3, 5-9, 12-19, 23, 25, 26, 28, 30, 32, 37, 38 and 118-120 under 35 U.S.C. § 103(a) be withdrawn.

Rejection of Claims 1-3, 5-19, 22, 23, 25-28, 30-32, 37, 38, and 118-120 under 35 U.S.C. § 103(a)

Claims 1-3, 5-19, 22, 23, 25-28, 30-32, 37, 38, and 118-120 are rejected under 35 U.S.C. § 103(a) as being unpatentable over '216, in view of '765, Koster, Li *et al.*, and DeJongh *et al.*, in further view of U.S. Patent No. 6,372,712 ('712), Kaneko *et al.* (Kaneko *et al.*, *Bioconjugate Chem.* (1991) 2, 133-141, Kratz *et al.* (*Arch. Pharm. Med. Chem.* (1998) 331, 47-53; and Beyer *et al.* (*J. Med. Chem.* (1998) 41, 2701-2708). Claims 22 and 31 have been cancelled, thus rendering their rejection moot.

Applicants respectfully traverse this rejection. Claims 1, 5, 30, and 37 and their dependent claims have been described above. The '216 reference, the '765 reference, Koster, Li *et al.*, and DeJongh *et al.* have also been described above. As discussed above, these references, alone or in combination, fail to teach or suggest the use of a negatively charged or neutral stabilizing group to reduce acute toxicity and, thus, fail to render obvious the presently claimed compounds..

The '712 patent, Kratz *et al.*, Beyer *et al.*, and Kaneko *et al.* are relied upon by the Examiner to provide examples of linkers between the tetrapeptide and the doxorubicin. However, none of these references, alone or in combination, make up for the deficiencies of the primary and secondary references described above. Indeed, these references also

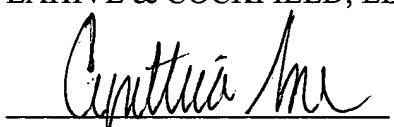
fail to teach or suggest the use of a negatively charged or neutral stabilizing group to reduce acute toxicity as claimed by Applicants.

For at least the foregoing reasons, Applicants respectfully request that this rejection of claims 1-3, 5-19, 22, 23, 25-28, 30-32, 37, 38, and 118-120 under 35 U.S.C. § 103(a) be withdrawn.

SUMMARY

It is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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